REMARKS

This responds to the Office Action mailed on June 25, 2009.

No claims are amended, no claims are canceled, and no claims are added; as a result, claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 are now pending in this application.

Response to Declarations

In his response to the declaration the Examiner acknowledged that the declarations were sufficient to overcome the rejection of the claims based upon Ma based on the persuasive arguments based upon evidence provided in the Cassidy and Jenkins declarations.

Nevertheless, the Examiner requested clarification of a minor peak on the chromatogram on p. 107 of the 10/27/2008 declaration ("the Cassidy declaration").

In response the applicants note that the retention time of the indicated peak is 8.83 min (with the smaller peak preceding it at 8.55 min) (as measured on the 252 nm chromatogram). On the accompanying 220 nm chromatogram on page 107 of the 10/27/2008 declaration, the corresponding peaks are at 8.85 min and 8.58 min. Neither of these retention times corresponds to the authentic target material retention time of 8.71 min.

§ 103 Rejection of the Claims

Claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ma et al (1995 Protein Peptide Letters 2:347-350; PTO 892 4/5/2006) in view of Tsunoda et al. (1996 Tetrahedron Letters 37:2457-2458; PTO 892 1/10/2007) or Tsunoda et al. II (1993 Tetrahedron Letters 34:1639-1642) as evidenced by the 1/21/2008 Jenkins declaration.

Applicants respectfully traverse the rejections, and request reconsideration and withdrawal of the rejections in light of the following arguments.

In raising the objection the examiner appears to argue that Tsunoda teaches that tosyl protection of the nitrogen instead of the Bzl protection of Ma is useful for Mitsunobu reactions, and that it would be obvious to make this modification to the Ma procedure. The examiner also

argues that, even if the Mitsunobu reaction with Tosyl protection did not work, according to the Jenkins declaration, aziridines may be opened by acidic sulfonamides and provide the 1,4-diazapan-2-one mimetic precursor via an alternative pathway.

Firstly, the applicant assumes that when the examiner refers to a Bzl (benzoyl) group, he actually refers to the Z (Cbz, benzyloxycarbonyl) group used in the Ma reference. It is the applicant's position, now recognized by the examiner in the withdrawn objections, that Ma did not in fact obtain the actual compound depicted in the document but rather had obtained an isomer that did not contain the seven membered ring. Given the relative difficulty in coming to this conclusion, the applicants submit that the skilled addressee would not be motivated to modify Ma based on Tsunoda as a skilled addressee would not realize they needed to! (Absent significant experimentation, a skilled addressee upon following Ma would assume they had obtained the product allegedly made by Ma (as evidenced by the fact the Ma authors themselves did not realize that they had the incorrect structure)).

Secondly, the applicant respectfully submits that the Tsunoda references in fact provide evidence that the desired Mitsunobu transformation is unlikely to proceed. In both papers, reaction of the N-Ts primary amine derivatives with a secondary alcohol (as present in the Ma publication) proceeds in significantly lower yields or requires much higher reaction temperatures than with unhindered primary alcohols (e.g. Tsunoda p. 2458 "3). The reaction of secondary alcohols needs higher temperatures to proceed, ..." Tsunoda II p. 1641 "However, *sec*-alcohols are much less reactive". However, none of the Tsunoda examples react a Ts-protected alpha-branched amine, as present in the Ma publication.

It is respectfully submitted that it is obvious to one skilled in the art that an alpha-branched amine would react much more slowly than an unbranched primary amine due to steric hindrance. Accordingly, when coupled with a secondary alcohol, one skilled in the art would expect the yields to be drastically reduced due to additional steric hindrance, to the point where the reaction would not be expected to proceed at all. Thus, the applicants of the present application submit that the Tsunoda references in fact teach that a Mitsunobu reaction of an alpha-branched amine with a secondary alcohol is unlikely to be successful, even with Ts protection. Furthermore, if the extended high temperatures (100 °C, 24h) employed in Tsunoda for secondary alcohols are required, one skilled in the art might expect to see decomposition of

the Boc protecting group present elsewhere on the Ma substrate. Accordingly, a skilled addressee would not be motivated to combine Tsunoda with Ma with any expectation that they would work.

Thirdly, the applicant respectfully disagrees with the premise that it would be obvious to use a tosyl protecting group to form a diazapanone system. Having established that a 3-membered aziridine is formed, there would be no expectation that altering the substituent would be able to overcome the overwhelming preference for forming three- or five- membered ring systems over seven-membered ring systems, as noted in the Jenkins declaration; thus it would not be obvious to one skilled in the art to attempt such a reaction. Furthermore, as noted in the Jenkins declaration, even if the alternate tosyl protecting group reaction was attempted, an aziridine or oxazoline ring system would likely be generated. It is not obvious to one skilled in the art as to which system is generated, as is made clear by the Jenkins declaration which states that "of the two possible structures that are proposed by Dr Cassidy, I am ***fairly*** certain that it is the N-Boc aziridine(4) that is formed." Thus, it is not obvious to one skilled in the art that this is in fact the intermediate obtained. Such a definitive statement simply cannot be made.

Given the uncertainty of whether an oxazoline or aziridine is obtained, it is not obvious that a tosyl protecting group would enable generation of the 7-membered ring system without knowledge of the 1999 Nouvet paper in which the diazapanone structure was apparently generated, as an oxazoline would be unlikely to be converted into the diazapanone. Furthermore, it is the position of the applicant that, even if it was thought that the aziridine structure was the intermediate that would be generated by using a tosyl protecting group, it is not obvious to one skilled in the art that the change in protecting group from Z to tosyl would result in ring-opening of the aziridine to form the diazepanone, as the difficulty in forming a 7-membered ring system would still take precedence over changes in protecting group. As the examiner himself states, "N-Boc aziridines ***MAY*** nevertheless be opened by acidic sulfonamides." Furthermore, if aziridine ring opening did occur, it could just as reasonably be expected by one skilled in the art to occur with attack at the other aziridine carbon centre, generating a 8-membered ring system rather than the diazapanone 7-membered ring system. It is impossible to predict the regiospecificity of the potential attack, as conformation preferences/hydrogen bonding could result in attack at either carbon center.

In summary, the applicant strongly believes that, given the incorrect structure is obtained originally in the Ma paper (which was not obvious to one skilled in the art at the time - either the original authors or the referees of the journal article), it is far from obvious to one skilled in the art that one could then generate the desired diazapanone through a non-disclosed and speculative alternative pathway.

Claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ma et al (1995 Protein Peptide Letters 2:347-350; PTO 892 4/5/2006) in view of Tsunoda et al. (1996 Tetrahedron Letters 37:2457-2458; PTO 892 1/10/2007) or Tsunoda et al. II (1993 Tetrahedron Letters 34:1639-1642) as evidenced by the 1/21/2008 Jenkins declaration further in view of Mammi et al. (1985 JACS 107:4008-4013).

Applicants respectfully traverse the rejections, and request reconsideration and withdrawal of the rejections in light of the following arguments.

The examiner argues that one of ordinary skill in the art would be motivated to generate an enkephalin analog of Mammi locked into place by an ethylene bridge in the manner of Ma et al, because the hydrogen bond is disrupted by water and analogs with additional restraints are desirable.

Given that this objection relies on Ma et al in view of Tsunoda, the applicant believes, due to the reasons outlined above, that the objection is without merit for the reasons previously discussed.

The applicant also argues that, in light of Mammi et al, it would not be obvious to replace the hydrogen bond disrupted by water with an ethylene bridge. Mammi et al disclose two hydrogen bonds in their enkephalin analog. Given that the analog retains high potency when tested in aqueous solution, when the hydrogen bond disrupted by water would be disturbed, it would more obvious to replace the other hydrogen bond with an additional restraint, thus locking the enkephalin analog into the active conformation seen in aqueous solution. The lack of obviousness to the approach proposed by the examiner is further supported by the many papers published since Mammi et al on enkephalin analogs which attempt to provide conformational

restraints by many different cyclization approaches, but not by replacement of the hydrogen bond. A recent example is Berezowska et al (Chem. Biol. Drug Des. 2009, 74, 329-334).

§ 112 Rejection of the Claims

Claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 113 and all dependent claims were rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections.

Applicants respectfully traverse the rejections, and request reconsideration and withdrawal of the rejections in light of the following arguments.

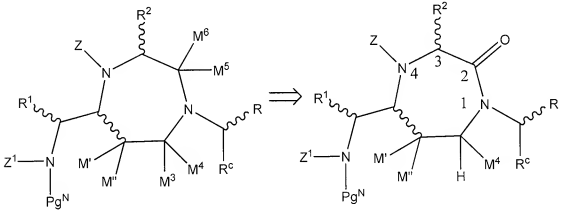
The omitted structural cooperative relationship concerns the definitions of M^4, R^C, R and Z.

a) in section (ii) of claim 113, $M^4 = M'$, it is not clear how this is possible and still be a 1,4-diazapan-2-one.

The applicants note that section (ii) of claim 113 states "M^3 is H and $M^4 = M'$, M^5 and M^6 when taken together with the carbon atom to which they are attached form a carbonyl group".

As a first point the applicant submits that the phrase "$M^4 = M''$" would be taken to mean that the M^4 substituent has the same values as the substituent M', namely that M^4 is selected from the group consisting of "hydrogen, C_1-C_4 alkyl, chloro and C_1-C_4 alkoxy" (as these are the potential values of M').

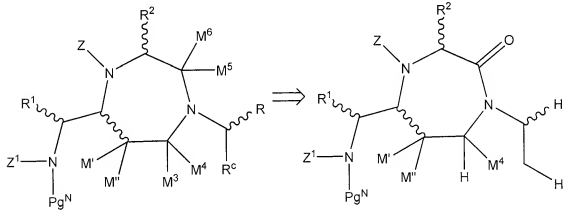
According to the definitions, "M' and M" may be the same or different and are selected from the group consisting of hydrogen, C_1-C_4 alkyl, chloro and C_1-C_4 alkoxy". It is submitted, therefore, that a skilled addressee would understand that, for example, when M^3 is H and M^5 and M^6 when taken together with the carbon atom to which they are attached form a carbonyl group, the following structure is obtained, which clearly contains the1,4-diazapan-2-one core:



Regardless of whether M', M" and M^4 = hydrogen, C_1-C_4 alkyl, chloro and C_1-C_4 alkoxy, the 1,4-diazapan-2-one structure remains.

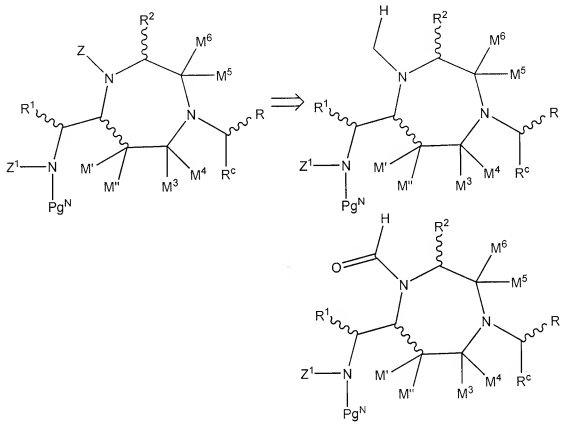
b) R^C is selected from the group consisting of CH_2R, which if R is H, the side chain of the amino acid glycine set forth in the structure it is not clear what structure is chemically possible.

The applicant notes that they once again submit that this would be clear to a skilled addressee. In the situation contemplated by the Examiner, R^C becomes CH_2H, or CH_3, a methyl group. If, at the same time, R = H, the diazapanone substituent becomes an ethyl group. These groups are chemically possible.



c) Z is selected from the group consisting of CH_2R and C(O)R and suffers similar issues as R^C

In these circumstances, if R = H, Z becomes CH_2H (CH_3), a methyl group, or it becomes C(O)H, a formyl group. Both groups are chemically possible.



d) Further compounding the confusion, the antecedent basis for R is ambiguous. R is set in the structure at a particular location (ca 4 O'clock) and is also defined as an amino acid side chain. It is not clear if the R in the definition for Z and R^C refer to the R of the structure or an amino acid side chain.

R as shown in the structure is defined directly as an amino acid side chain group in the text ("R, R^1 and R^2 are amino acid side chain groups which may be the same or different;"), and further references to R such as, for example, in the definition of R^C and Z, refer to the same definition. It is submitted that this would be clear to a skilled addressee in the art.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone the undersigned at (612) 373-6941 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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Date: October 20, 2009

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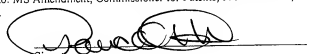
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